Threats to the effectiveness of insecticide-treated bednets for malaria control: thinking beyond insecticide resistance

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From 2004 to 2019, insecticide-treated bednets (ITNs) have been the most effective tool for reducing malaria morbidity and mortality in sub-Saharan Africa. Recently, however, the decline in malaria cases and deaths has stalled. Some suggest that this inertia is due to increasing resistance in malaria vectors to the pyrethroid insecticides used for treating ITNs. However, there is presently little evidence to reach this conclusion and we therefore recommend that a broader perspective to evaluate ITN effectiveness in terms of access to nets, use of nets, bioefficacy, and durability should be taken. We argue that a single focus on insecticide resistance misses the bigger picture. To improve the effects of ITNs, net coverage should increase by increasing funding for programmes, adopting improved strategies for increasing ITN uptake, and enhancing the longevity of the active ingredients and the physical integrity of nets, while simultaneously accelerating the development and evaluation of novel vector control tools.

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Introduction

From 2004 to 2019, a major malaria control campaign based on insecticide-treated bednets (ITNs), indoor residual spraying (IRS), and prompt and effective treatment with antimalarials, prevented an estimated 1·2 billion malaria cases and 7·1 million deaths in sub-Saharan Africa.[1] By far the most important contribution was due to ITNs, responsible for an estimated 68% of the cases averted.[2] The scale of their deployment in sub-Saharan Africa has been huge, with 1·9 billion ITNs supplied to the region from 2004 to 2019.[1] Despite this massive roll-out, in 2019, only 36% of households owned at least one bednet for every two persons, increasing from a mere 1% in 2000. Although still falling well short of the target of providing protection against malaria for all who are at risk, this coordinated campaign has been a remarkable achievement. Unfortunately, since 2015, the decline in malaria has stalled, with WHO's African region failing to meet the 2020 Global Technical Strategy milestones for malaria morbidity by 37% and malaria mortality by 25%.[1] A major concern has been that resistance to insecticides used on the nets in malaria mosquitoes has caused the decline in malaria to plateau. Consequently, WHO has focused considerable efforts to monitor the presence of insecticide resistance in vector populations around the globe.[3] Further, the threat of resistance has shaped international malaria control policy, and drives much of the investment in research and development for vector control tools, eclipsing other factors that also affect the effectiveness of ITNs. In this Viewpoint, we aim to broaden discussion beyond the single threat of resistance and stimulate consideration of a more comprehensive suite of factors that affect the current effectiveness of ITNs and contribute to the stalling progress towards malaria eradication. Technical terms used in the article are explained in panel 1 and how ITNs work in panel 2.

Insecticide resistance

Until the last very years, the only insecticides used for ITNs were pyrethroids, such as permethrin and deltamethrin, which are highly lethal to susceptible mosquitoes after even transient contact. Evolutionary theory, however, tells us that sustained use of a toxic substance that reduces the fitness of an organism will probably select for resistance. Over time, providing the toxin pressure is maintained, resistant individuals will spread through the population. In line with this expectation, resistance against pyrethroid insecticides was first detected in *Anopheles gambiae*, sub-Saharan Africa's principal malaria vector, in Côte d'Ivoire in 1993,[4] and is now widespread throughout the region. There are few, if any countries, where malaria vector populations remain fully susceptible.[5]

The effect of pyrethroid resistance on malaria control has been a primary concern for over 20 years.[6] Yet in spite of the rapid and predictable evolution of resistance in response to widescale deployment of ITNs, evidence of control failure due to physiological resistance against ITNs is mixed. Many laboratory and semi-field studies show that ITNs have less instantaneous effect on mortality and blood feeding of resistant mosquitoes than susceptible populations.[7,8] These entomological studies provide valuable insights into the potential effect of resistance on performance of ITNs, but they do not tell us what the effect of resistance might be on overall malaria transmission at the community level. To address this limitation one study[9] used entomological data from multiple small scale, short-term experiments to parameterise a mathematical model of transmission. The study[9] suggested that increasing levels of resistance in vector populations would increase both the number of clinical malaria cases and the force of infection. The magnitude of the effect, however, was sensitive to the effective coverage of ITNs (ie, what proportion of the population owned and used a net). This result was further supported by a separate modelling study that indicated that at moderate levels of effective coverage (ie, >50%), the effect size of resistance on overall transmission could be very small.[10] Therefore, although laboratory and semi-field studies raise justifiable concern, how resistance plays out at community level in

Panel 1: Glossary of terms

Definitions used by WHO

- Bioefficacy: refers to insecticidal activity and is a measure of knockdown, mortality, or inhibition of blood feeding induced in mosquitoes recorded in a WHO test such as a cone bioassay or tunnel test.
- Durability: considers the combination of net survivorship, fabric integrity, and insecticidal activity (bioefficacy).
- Effective coverage: is the fraction of the population that use insecticide-treated bednets.
- Entomological inoculation rate: number of infective bites received per person in a given unit of time in a human population.
- Functional survival: is the proportion of insecticide-treated bednets in good or acceptable condition at time (x) expressed as a percentage of insecticide-treated bednets originally received and not given away at time (x).
- Insecticide resistance: property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation.
- Insecticidal activity (bioefficacy): is the degree of knockdown, mortality, or inhibition of blood feeding induced in susceptible mosquitoes, as determined by standard WHO test procedures and criteria (ie, cone bioassay and tunnel test). Insecticidal activity is associated with the type and content or availability of insecticide. The insecticide content is expressed as g/kg or mg/m^2 of the insecticide-treated bednets and is determined by the method outlined in WHO specifications for insecticide-treated bednets. This information is of value in interpreting data on bioefficacy. Insecticidal activity can be assessed as a function of length of use.
- Knockdown: for insecticide bioassays, a knockdowned mosquito is one that cannot stand (eg, has one or two legs), cannot fly in a coordinated manner, lies on its back, moving legs and wings but unable to take off or one that can stand and take off briefly but falls down immediately.
- Mortality: for insecticide bioassays, it is a mosquito that shows no sign of life, is immobile and cannot stand.
- Physical (fabric) integrity: reflects the number, location, and size of holes in each net.
- Survivorship: is the proportion of distributed nets still available for use as intended in the households to which they were given after a defined period (eg, 1, 2, or 3 or more years).
- Universal coverage: is access to and use of nets by the entire population at risk of malaria.

the field is less clear. This conclusion is further supported by epidemiological data from sub-Saharan Africa.[11-13]

To date, there are no convincing examples of insecticide resistance rendering ITNs ineffective in sub-Saharan Africa. In 2014, a systematic review and meta-analysis[14] of 36 laboratory and 24 field studies found that ITNs were more effective than untreated bednets irrespective of the level of resistance. A similar analysis[15] published in 2019 reported a 60% reduction in the odds of malaria associated with ITN use.[15] A study in Malawi showed that net use was associated with a 30% reduction in the incidence of malaria infection compared to non-net use, despite high levels of insecticide resistance in the major malaria vectors.[11] In Kenya, net users were also protected with 39% lower infection rates in areas of low resistance and 45% lower in high resistant areas, than were non-net users.[12]

The largest and most comprehensive study[13] to date was a WHO-led multi-country study done in Benin, Cameroon, India, Kenya, and Sudan. Approximately 40 000 children were followed up and the vector control tool used was ITNs, apart from Sudan where ITNs were combined with indoor residual spraying. Children who slept under ITNs had a 37% reduced risk of infection with *Plasmodium falciparum* and 38% lower incidence of clinical malaria than did non-users across a range of different insecticide intensities. There was no evidence of an association between levels of insecticide resistance and protection against malaria provided by nets. Again, the conclusion is that ITNs continue to provide control benefits for users in spite of insecticide resistance.

Two randomised controlled trials[16,17] have been done in areas with high levels of insecticide-resistant vectors, using next generation ITNs with novel modes of action designed to mitigate pyrethroid resistance. In Tanzania, a trial[16] of nets with a pyrethroid plus piperonyl butoxide, a synergist that disrupts the capacity of mosquitoes to detoxify pyrethroids, showed a 63% reduction in the odds of malaria infections compared with pyrethroid only nets. In Burkina Faso, a trial[17] of nets with a pyrethroid plus pyriproxyfen, an insect growth regulator, showed enhanced protection against clinical malaria than with conventional pyrethroid nets.[17] Taken at face value, these results might suggest that the combination nets are resistance-breaking and thereby provide a measure of the effect of resistance on control with standard nets. An alternative, and more parsimonious explanation, is that the combination nets are simply more toxic than pyrethroids alone and would be similarly efficacious if used against susceptible (or resistant) vector populations. For example, when a susceptible strain of the mosquito, *Culex pipiens pallens*, was tested against a range of pyrethroids, knockdown and mortality increased sharply with the addition of piperonyl butoxide.[18] Moreover, the combination nets used in these field trials[19,20] had increased bioavailability of the pyrethroid on the net surface compared with the standard net. The combination nets tested to date are likely to be more insecticidal than standard ITNs, irrespective of whether the vectors are resistant or susceptible.

Why ITNs can remain protective against resistant mosquitoes

The evidence taken together suggests that insecticide resistance is not presently having a substantial effect on malaria control. Why might this be the case? First, intact ITNs are a physical barrier to mosquitoes and even untreated nets provide personal protection against malaria provided they are undamaged.[21] Second, there may be sublethal effects of exposure to pyrethroids, such as increased irritancy on contact with treated netting, decreasing the exposed mosquito's ability to find and feed on a host,[10] or incubate malaria parasites.[22,23] Third, resistance might reduce vector competence in the absence of insecticide exposure with malaria infection reducing survival only in insecticide-resistant mosquitoes, but not in susceptibles.[24,25] Fourth, resistant mosquitoes can be

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less fit than susceptible ones,[26,27] reducing their overall survival, and hence reducing the number of older and therefore infective mosquitoes. Overall, these factors operate to produce complex interactions that are likely to dilute the effect of insecticide resistance on the effectiveness of ITNs.

The way insecticide resistance is commonly assessed might further obscure the demonstration of a link between resistance and effect on vector control. WHO's standard discriminating dose bioassay[28] is designed to detect the early stages of resistance in vector populations, not to infer anything about implications for control. The standard assays expose 3–5-day-old, non-blood-fed mosquitoes in a small tube lined with paper treated with insecticide at twice the concentration required to kill 100% of susceptible mosquitoes. After 60 min exposure the mosquitoes are removed and assessed for mortality, and then assessed again after 24 h. A mosquito population is characterised as resistant if it displays less than 90% mortality at 24 h. In real life, mosquitoes vary in age, blood-feeding status and frequency and intensity of previous exposure to insecticide. Video studies[29] on mosquitoes approaching a human-occupied net show that mosquito contact with an ITN is brief, with an average duration of 7 s—orders of magnitude shorter than the WHO bioassay. Additionally, mosquitoes contact the net differently as they land and attempt to feed and can contact a treated net on multiple occasions over their lifetime. The net itself has a higher dose of insecticide than used in the tube test (although this will vary depending on the age of the net and the wash history). To assess these effects studies[30] have attempted to develop more realistic assays that allow mosquitoes to search for a host and contact an ITN on multiple occasions.[30] This research suggests that substantial mortality can occur even in highly resistant mosquitoes, which can reduce their blood-feeding success. Using transmission models to explore these phenomena reveals that even small effects can aggregate over the lifetime of a mosquito to substantially reduce malaria transmission potential of resistant mosquitoes.[10] Furthermore, WHO bioassays should be done at 25 °C ± 2 °C.[28] At over 30°C, temperatures frequently found in African houses, pyrethroid-resistant mosquitoes can become more susceptible.[31] These findings suggest that although standard assays might be valuable as resistance surveillance tools, they provide little insight into the functional significance of this resistance. Therefore, simply characterising a population as resistant according to the WHO test criteria does not mean there are necessarily any consequences for the effectiveness of ITNs.

The evidence suggests that in spite of widespread resistance, pyrethroid-treated nets remain an important intervention against malaria in sub-Saharan Africa. This observation does not mean that resistance has no effect; some of the data referred to above suggest that resistance-breaking insecticide mixtures on nets do provide improved protection compared with standard nets (although as we indicate it is possible to explain this without necessarily invoking resistance). Nonetheless, the epidemiological effect size appears small and we question whether our understandable concern about insecticide resistance has distracted attention from other aspects of ITNs and their use that are potentially more important in limiting effect of ITNs, such as inadequate funding leading to declining access to and use of nets, product quality and basic bioefficacy, net durability, and residual transmission.

Panel 2: How insecticide-treated bednets work

Bednets work by providing a physical barrier to reduce mosquito–human contact and successful blood feeding. This is true whether the net is treated with insecticides or not. Adding insecticides provides additional protection in at least three ways. First, contact with the insecticide can kill the mosquito or rapidly disorient it, reducing the potential for mosquitoes to keep searching around the net and potentially feed on a human that might inadvertently have part of their body resting against the net as they sleep. Second, the death or impairment reduces the chances of the mosquito getting into a net, if the net is not properly tucked in under a mattress, or through a hole when the net inevitably becomes damaged. Third, killing or disorienting mosquitoes prevents them from going on to bite people who do not have nets or at times when people are not using nets. This latter effect can provide a level of community protection above and beyond the personal protective effects as long as effective coverage is high enough. Other effects might result from these primary effects (especially at high insecticide-treated bednets coverage), including reductions in density of adult mosquitoes or changes in mosquito population age structure. Skewing age structure towards younger mosquitoes can have a marked effect on transmission potential because it typically takes around 10–12 days for malaria parasites to complete development within the mosquito after an initial infectious blood meal. Repeat exposure to insecticide-treated bednets over successive blood feeding cycles reduces the proportion of mosquitoes that live long enough to successfully incubate the parasite, this can reduce transmission potential even if overall mosquito density remains relatively unchanged. Sublethal effects such as reduced feeding propensity, reduced host-searching capacity, or delayed mortality could also accrue following initial insecticide exposure; such effects might be important in contributing to control of mosquitoes that exhibit reduced mortality due to resistance.

ITN effective coverage, bioefficacy, fabric integrity, and residual transmission

A principal aim of ITN distribution programmes is to get at least 80% of the at-risk population sleeping under a net. With high ITN coverage, daily survival of vectors reduces substantially providing a community effect[32-34] that will reduce the number of infective mosquitoes and thereby protect non-net users, as well as ITN users. Unfortunately, the main reason that nets appear to fail in so many places is because people do not have access to a net. In 2019, only 36% of households had at least one net for every two persons, and 52% of people in at-risk areas had access to a net.[1] Worryingly, net coverage peaked in 2017, and has declined thereafter (figure A). Moreover, ITN coverage is highly heterogeneous across the region (figure B). Because of the decline in coverage of protection against malaria in at risk populations, it is

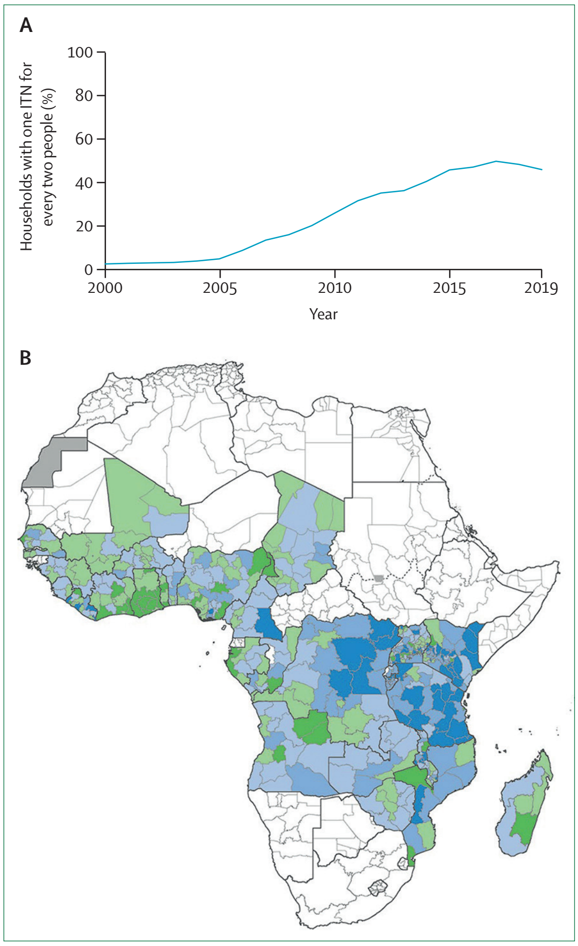

Figure: **ITNs coverage in sub-Saharan Africa**
(A) Graph showing the proportion of households with one net for every two people from 2000 to 2019. (B) Map of Africa showing distribution of insecticide-treated bednets use by children younger than 5 years.[1] ITN=insecticide-treated bednets.

surprising that the downward trends in malaria case numbers and deaths have not started to reverse. The reason for this decline in coverage is that funding for malaria control globally has stagnated at about US$3 billion per year since 2012, whereas populations at risk and unit costs increased. It is remarkable how much has been achieved with this rather modest spending on a major global disease. Unsurprisingly, the COVID-19 pandemic has led to major disruptions in malaria control in 2020,[35,36] and this is likely to continue until vaccines are rolled out globally.

Adequate numbers of nets means at least one net shared between no more than two people. Assuming this metric is a realistic measure of access, in larger households with many adults and teenagers, one net per two people will be inadequate. It is also compounded by the notoriously difficult task of determining whether people actually sleep under a net or not. Self-reporting is likely to overestimate actual net usage. Therefore, coverage is not just an issue about a person having access to a net, but it is also whether they will use the net or not. The most common reasons for not using a net are that there are too few nets in the household, sleeping under a net feels too hot, or there are too few mosquitoes to bother.[37] Bedrooms can be cooled by installing at least two large, screened windows in opposite walls.[38] Low net use when mosquito densities are low is a challenge if malaria elimination is the goal. A study in Uganda[39] showed after a major reduction in malaria caused by a combination of IRS and ITNs, non-adherence to net use and ITNs was more common when mosquito numbers were low; in poorer households; and in households with children, particularly those of school age, which is the population that harbour the most malaria parasites. Health promotion targeted at this age group could help reduce the burden of malaria further. In parts of sub-Saharan Africa, insecticide resistance in bedbugs lowers compliance,[40,41] so bedbug control with alternative products[42] could increase coverage. These examples serve to illustrate the importance of understanding local obstacles to effective coverage. To increase access to and use of nets, deployment needs to be adapted to local conditions.

Of major concern is the deployment of sub-standard ITNs. A study[43] from Papua New Guinea, where vectors remain susceptible to pyrethroids, investigated the relative effect of ITNs manufactured from 2007 to 2019 on local vectors.[43] All nets manufactured from 2007 to 2012 met the required WHO standard of knockdown and killing, compared with only 17% of nets manufactured from 2013 to 2019. The authors suggested that malaria resurgence in Papua New Guinea might be due to sub-standard nets used after 2013. Papua New Guinea is not alone in being supplied sub-standard nets, as they have also been reported in Burkina Faso in 2010,[44] in the Solomon Islands in 2014,[45] and Rwanda in 2015.[46]

For ITN brands to be approved for malaria control they must be evaluated by WHO's prequalification team (previously named WHO's Pesticide Evaluation Scheme). 20 brands of long-lasting insecticidal nets are currently prequalified as vector control products by WHO. Insecticidal nets are classified as long-lasting insecticidal nets if: (1) a net washed 20 times results in 80% or higher mortality or 95% or higher knockdown in WHO cone tests, (2) they are not inferior to a reference net when washed 20 times in terms of blood-feeding inhibition and mortality in experimental huts, and (3) they are effective for at least 3 years in the field (ie, in serviceable condition passing bioefficacy and fabric integrity criteria).[47] In practice, most nets do not last 3 years in the field. Net surveys in 13 countries indicate median functional survivorship of 40% (IQR 33–55; n=9), 36 months after deployment (table). These findings suggest that more than half of nets fail long before they are replaced and there are too few people with access to effective ITNs. The real-world durability data suggest the need for improved product testing and rigorous quality

	Location	Insecticide-treated net brand	Active ingredient	Functional survivorship*	Time functional survivorship recorded after distribution (months)†
Mansiangi and colleagues, 2020[48]	Burkina Faso	Olyset	Permethrin	12%	36
Mansiangi and colleagues, 2020[48]	Democratic Republic of the Congo	DuraNet	Alpha-cypermethrin	37%	31
Abílio and colleagues, 2020[49]	Democratic Republic of the Congo	DawaPlus 2.0	Deltamethrin	17%	31
Abílio and colleagues, 2020[49]	Inhambane, Mozambique	Royal Sentry	Alpha-cypermethrin	57%	36
Abílio and colleagues, 2020[49]	Nampula, Mozambique	Royal Sentry	Alpha-cypermethrin	33%	36
Obi and colleagues, 2020[50]	Tete, Mozambique	MAGNet	Alpha-cypermethrin	43%	36
Obi and colleagues, 2020[50]	Ebonyi, Nigeria	DawaPlus 2.0	Deltamethrin	55%	36
Obi and colleagues, 2020[50]	Oyo, Nigeria	DawaPlus 2.0	Deltamethrin	75%	24
Obi and colleagues, 2020[50]	Zamfara, Nigeria	DawaPlus 2.0	Deltamethrin	80%	36
Haji and colleagues, 2020[51]	Tanzania	Olyset	Permethrin	55%	33
Haji and colleagues, 2020[51]	Tanzania	PermaNet 2.0	Deltamethrin	51%	33
Lorenz and colleagues, 2020[52]	Tanzania	Olyset	Permethrin	27%	36
Lorenz and colleagues, 2020[52]	Tanzania	PermaNet 2.0	Deltamethrin	38%	36
Lorenz and colleagues, 2020[52]	Tanzania	NetProtect	Deltamethrin	40%	36

*Number of months after deployment functional survivorship reported. †Functional survivorship is the proportion of nets in serviceable condition, excluding those lost by attrition. Months when net first fails WHO bioefficacy criteria (≥80% mortality or ≥95% knockdown).

Table: **Nets serviceable after 2–3 years of use**

assurance to maintain performance. There are currently very few data on the durability of new multiple insecticide nets under real-life conditions,[53] and their potential superiority over standard nets might be only transient if they fail too quickly under conditions of everyday wear and tear. There has been a recent appeal to develop more durable mosquito nets,[54] which we strongly endorse. Companies should be incentivised to develop more durable nets and provide evidence from the field supporting their claims. Although the unit price of more durable nets might exceed that of their more flimsy counterparts, the cost per year of protection could probably make them more cost-effective.

It is also important to reemphasise the interaction between coverage and bioefficacy, which links to the functional significance of insecticide resistance discussed earlier.[10] If there is high effective coverage then even a relatively ineffective net (one that is less insecticidal, such as could occur with resistance) can still be effective at reducing community transmission. Alternatively, lower coverage of highly insecticidal nets can achieve the same result. The worst scenario is low coverage of weakly insecticidal nets.

The antimalarial efficacy of ITNs is primarily dependent on their ability to protect people when they are indoors and in bed. Mosquito biting that takes place outdoors either because mosquitoes take blood meals in the early evening before people are in bed, or because of changes in human night-time behaviour, contributes to residual transmission which limits the effectiveness of vector control with ITNs. A systematic review[55] of mosquito and human behaviour concluded that although most biting by major malaria vectors occurred during times when people are in bed and hence able to protect themselves by means of an ITN, the proportion of transmission due to outdoor biting has increased since 2000. Much of this outdoor transmission is the result of changes in human behaviour related to certain occupations, sociocultural events, entertainment, household chores, and sleeping outdoors during travel.[56,57] Residual transmission has been noted to limit the maximum effectiveness of both ITNs and indoor residual spraying, even in settings where they have been deployed to scale.[58,59] Elimination of malaria might therefore be dependent on the development, evaluation, and implementation of new classes of vector control tools that can better control both indoor and outdoor transmission. Such new tools might be especially important in situations where behavioural resistance has evolved, wherein mosquito populations exhibit a shift in biting or resting behaviour thereby reducing their exposure to indoor interventions such as ITNs and indoor residual spraying.[60-62]

Recommendations

We suggest six recommendations for improving the effectiveness of ITNs. First, WHO should establish a mechanism for the post-market monitoring of approved ITNs to ensure ITN quality is maintained. Second, national malaria control programmes should evaluate the functional quality of nets with each large consignment of ITNs. Third, head-to-head comparisons of different ITN brands should be done regularly, with different net brands randomly distributed among the study population.[52] Fourth, when awarding grants for purchasing ITNs, The Global Fund to Fight AIDS, Tuberculosis and Malaria should use a metric that includes net coverage and access, and length of protection offered, not just cost price of nets, thereby incentivising manufacturers to improve the quality and durability of nets. Fifth, academics and policy makers should look beyond insecticide resistance as a threat to malaria control and consider effective coverage, bioefficacy, net durability, and residual transmission. Last, global funding for malaria control needs to increase substantially to not only keep pace with population growth in malaria endemic countries and inflation of costs of malaria commodities, but also to get back on track with the targets set by the WHO Global Technical Strategy.

Conclusions

There is limited evidence, at present, that insecticide resistance in relation to ITN use is primarily responsible for the failure to effectively control or eliminate malaria in sub-Saharan Africa. Resurgence of malaria is more likely to be the result of inadequate funding leading to low net coverage and use, reduced bioefficacy of standard nets, poor and possibly deteriorating net durability, and increased risk of infection due to changing human and mosquito behaviour. New generation bednets using chemical combinations look promising and provide better protection against malaria than standard pyrethroid only nets. Importantly, we should explore novel ways for improving net coverage and carry out quality control after market approval to ensure that standards of ITNs are maintained in the field. Improved net durability needs to be urgently addressed, even if higher quality nets are more expensive. National control programmes are encouraged to develop novel ways to increase net use and identify sub-standard ITNs. Insecticide resistance is only one of the threats to effective malaria control with ITNs, and possibly not the most pressing one.

Contributors

SWL, MBT, and IK contributed to the planning of the manuscript: all discussed the content and SWL wrote the first draft. All authors contributed equally to the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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